INDOLE DERIVATIVES

CVII.* GENERAL METHOD FOR THE PREPARATION OF α-(3-INDOLYL) ALIPHATIC ACIDS

V. S. Rozhkov, Yu. I. Smushkevich,
and N. N. Suvorov

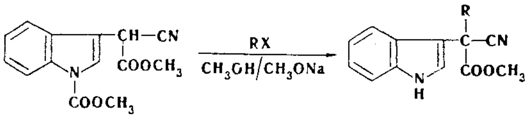
UDC 547.754.757

A method for the preparation of α-(3-indolyl) aliphatic acids, including those containing functional groups (COOH, C≡N), which is based on alkylation of N-carbomethoxy-3-indolylcyanoacetic ester, was developed.

Derivatives of aryl aliphatic acids of the ArCH(R)COOH type constitute an important group of pharmaceutical preparations that have cholinolytic activity [2].

Their indole analogs have not been studied due to the lack of a general method for their preparation. A method for the preparation of aryl aliphatic acids was based on alkylation of arylacetonitriles with halo derivatives, most often in the presence of an alkali metal amide. A disadvantage of this method is the formation of a mixture of mono- and dialkylation products. This obstacle can be overcome to a considerable extent by the use of "extractive" alkylation [3]. However, the extension of this method to the indole series is complicated by the possibility of the formation of N-alkylation products.

The introduction of a carbomethoxy group into the side chain of indolylacetonitrile considerably facilitates alkylation of the side chain, and alkylation occurs even in alcohol solution in the presence of sodium alkoxide, i.e., under conditions where nitrogen alkylation is not observed. Alkylation of N-carbomethoxy-3-indolylcyanoacetic ester (I), which we have previously obtained, makes it possible to avoid the formation of di- and N-alkylation products. Cyanoacetic ester I is readily alkylated by primary halo derivatives of various types (R = alkyl, allyl, and benzyl) to give α-cyano-α-(3-indolyl) aliphatic acid esters IIa-d. It should be noted that splitting out of the carbomethoxy group from the nitrogen of the indole ring occurs during the reaction.



I

II.a-f

III a $R=CH_3$; b $R=C_6H_5—CH_2$

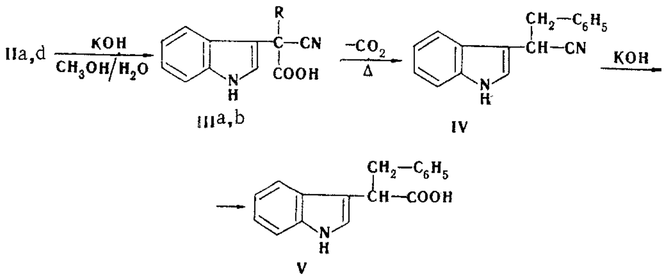
The mild alkylation conditions make it possible to obtain α-cyano-α-(3-indolyl) aliphatic acid esters containing functional groups, for example, carbomethoxy and nitrile derivatives IIe and IIf. Hydrolysis and decarboxylation of esters II makes it possible to convert them to nitriles (IV) of α-(3-indolyl) aliphatic acids and to pass from them to the acids themselves (V).

Thus alkylation of cyanoacetic ester I is a convenient general method for the preparation of α-(3-indolyl) aliphatic acids.

---

*See [1] for communication CVI.

D. I. Mendeleev Chemical-Engineering Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 942-945, July, 1975. Original article submitted June 25, 1974.



X = halogen; II a $R=CH_3$; b $R=C_2H_5$; c $R=CH_2=CH-CH_2$; d $R=C_6H_5-CH_2$; e $R= =CH_2-COOCH_3$; f $R=CH_2-CH_2-CN$

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with UR-10 or UR-20 spectrometers. The UV spectra of ethanol solutions were recorded with a Specord spectrophotometer. The spectra were recorded with a JNM-4H-100 spectrometer on the δ scale with tetramethylsilane as the internal standard.

Methyl α-Cyano-α-(3-indolyl)propionate (IIa). A 2.72-g (0.010 mole) sample of cyanoacetic ester I was added to a hot solution of sodium methoxide obtained from 0.3 g (0.013 mole) of Na and 15 ml of methanol, after which 1.7 g (0.012 mole) of methyl iodide was added dropwise, and the mixture was heated with stirring for 30 min. It was then cooled, the methanol was removed by vacuum distillation, 50 ml of water was added, and the product was extracted with three 50-ml portions of ether. The extract was washed with three 50-ml portions of water and dried with anhydrous $MgSO_4$. The ether was then removed by distillation, and the residue was recrystallized from aqueous methanol to give 1.8 g (83%) of ester IIa with mp 160-162°. Found: C 68.5; H 5.3; N 12.4%, $C_{13}H_{12}N_2O_2$. Calculated: C 68.5; H 5.3; N 12.3%. IR spectrum: 1725 (C=O), 2260 (C≡N), and 3400 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 217 (4.60); 270 (3.86); 278 (3.86); 287 nm (3.81). PMR spectrum (in $CDCl_3$): s* 2.14 (CH_3), s 3.88 ($C-O-CH_3$), and s 8.62 (NH).

Methyl α-Cyano-α-(3-indolyl)butyrate (IIb). This compound was similarly obtained from 2.72 g (0.010 mole) of cyanoacetic ester I, 0.3 g (0.013 mole) of Na in 50 ml of methanol, and 1.9 g (0.012 mole) of ethyl iodide. The yield of ester IIb, with mp 87-89°, was 1.4 g (58%). Found: C 69.1; H 5.8; N 11.3%. $C_{14}H_{14}N_2O_2$. Calculated: C 69.4; H 5.8; N 11.6%. IR spectrum: 1740 (C = O), 2260 (C ≡ N), 3400 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 217 (4.58); 270 (3.83); 278 (3.83), 287 nm (3.80). PMR spectrum (in $CDCl_3$): t 1.14 (CH_2CH_3), m 2.46 (CH_2CH_3), s 3.80 ($CO-OCH_3$), and s 8.60 (NH).

Methyl α-Cyano-α-(3-indolyl)penten-4-oate (IIc). This compound was similarly obtained from 2.72 g (0.010 mole) of cyanoacetic ester I, 0.3 g (0.013 mole) of Na in 15 ml of methanol, and 1.45 g (0.012 mole) of allyl bromide. The yield of ester IIc, with mp 88-90°, was 1.7 g (67%). Found: C 70.8; H 5.6; N 10.9%. $C_{15}H_{14}N_2O_2$. Calculated: C 70.8; H 5.5; N 11.0%. IR spectrum: 1650 (C=C), 1725 (C=O), 2255 (C≡N), 3400 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 217 (4.60); 270 (3.85); 278 (3.85); 287 nm (3.82). PMR spectrum (in $CDCl_3$): m 3.48 ($CH_2CH = CH_2$), s 3.88 ($CO-OCH_3$), m 5.44 ($CH_2CH = CH_2$), m 6.0 ($CH_2CH = CH_2$), and s 8.62 (NH).

Methyl α,γ-Dicyano-α-(3-indolyl)butyrate (IIf). This compound was similarly obtained from 2.72 g (0.010 mole) of cyanoacetic ester I, 0.3 g (0.013 mole) of Na in 15 ml of methanol, and 1.6 g (0.012 mole) of β-bromopropionitrile. The yield of ester IIf, with mp 111-113°, was 1.6 g (60%). Found: C 67.4; H 5.0; N 15.8%. $C_{15}H_{13}N_3O_2$. Calculated: C 67.4; H 4.9; N 15.7%. IR spectrum: 1755 (C=O); 2260 (shoulder) (C≡N), 2270 (C≡N), 3360 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 217 (4.67); 270 (3.93); 278 (3.93); 287 nm (3.90). PMR spectrum (in $CDCl_3$): t 2.50 (CH_2CH_2CN), t 2.80 (CH_2CH_2CN), s 3.80 ($COOCH_3$), and s 8.80 (NH).

Methyl α-Cyano-α-(3-indolyl)-β-phenylpropionate (IId). A 2.72-g (0.010 mole) sample of cyanoacetic ester I was added with stirring to a hot solution of sodium methoxide obtained from 0.3 g (0.013 mole) of Na in 20 ml of methanol, after which 1.52 g (0.012 mole) of benzyl chloride was added with stirring and heating, and the mixture was stirred and heated for 30 min. It was then cooled, and the resulting precipitate was removed by filtration and washed with a small amount of aqueous methanol (1:1) and ether to give 2.4 g (79%) of ester IId with mp 156-158° (from aqueous methanol). Found: C 74.5; H 5.4; N 9.0%.

---

*Here and subsequently, s is singlet, t is triplet, q is quartet, and m is multiplet.

$C_{19}H_{16}N_2O_2$. Calculated: C 75.0; H 5.3 ; N 9.2%. IR spectrum: 1725 (C=O), 2250 (C≡N), 3360 cm^{-1} (NH). UV spectrum, λ_{max}, (log ε): 217 (4.64); 270 (3.86); 278 (3.86); 287 nm (3.83). PMR spectrum (in $CDCl_3$): q 3.70 ($CH_2C_6H_5$), s 3.70 ($CO-OCH_3$), and s 8.45 (NH).

Dimethyl α-Cyano-α-(3-indolyl)succinate (IIe). The method used to prepare IId was used to obtain this compound from 2.72 g (0.010 mole) of cyanoacetic ester I, 0.3 g (0.013 mole) of Na in 20 ml of methanol, and 1.85 g (0.012 mole) of methyl bromoacetate. The yield of IIe, with mp 177-178° (from methanol), was 2.3 g (81%). Found: C 63.0; H 5.0; N 9.8%. $C_{15}H_{14}N_2O_4$. Calculated: C 63.0; H 4.9; N 9.8%. IR spectrum: 1725, 1740 (C=O), 2260 (C≡N), 3440 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 217 (4.46); 270 (3.76); 278 (3.76); 287 nm (3.71).

α-Cyano-α-(3-indolyl)propionic Acid (IIIa). A solution of 1.4 g (0.025 mole) of KOH in 5 ml of water was added to 2.3 g (0.010 mole) of ester IIa in 10 ml of methanol, and the mixture was stirred at room temperature for 2 h. It was then cooled, acidified with concentrated HCl, and extracted with three 50-ml portions of ether. The ether extract was washed with three 50-ml portions of saturated NaCl solution and dried with anhydrous $MgSO_4$. The ether was then removed by distillation to give 1.5 g (70%) of acid IIIa as a colorless oily liquid. Acid IIIa was characterized in the form of the S-benzylthiuronium salt with mp 185-186° (dec., from aqueous methanol). Found: C 63.0; H 5.5; N 14.8%. $C_{20}H_{20}N_4O_2S$. Calculated: C 63.1; H 5.3; N 14.8%.

α-Cyano-α-(3-indolyl)-β-phenylpropionic Acid (IIIb). A solution of 1.4 g (0.025 mole) of KOH in 5 ml of water was added to 3.0 g (0.01 mole) of ester IId in 10 of methanol, after which the mixture was refluxed for 15 min. It was then cooled and acidified with 8 ml of concentrated HCl. When the mixture was stirred, acid IIIb precipitated; it was removed by filtration, washed with water, and dried at room temperature to give 2.6 g (90%) of acid IIIb. Recrystallization from benzene–petroleum ether gave a product with mp 125-127° (dec., loss of benzene) that contained crystallization benzene; mp 185-187° (dec., decarboxylation). Found: C 78.6; H 5.6; N 7.5%. $C_{18}H_{14}N_2O_2 \cdot C_6H_6$. Calculated: C 78.2; H 5.4; N 7.6%. IR spectrum: 1715, 1730 (C=O), 2260 (C≡N), 2500-2700 (COOH), 3430 cm^{-1} (NH).

α-(3-Indolyl)-β-phenylpropionylnitrile (IV). A 2.9-g (0.01 mole) sample of acid IIIb was decarboxylated in a test tube in a gentle stream of argon by immersion in a metal bath at 220-230° for 15-20 min. The product was cooled and purified by passing through a 1 by 15 cm column containing Al_2O_3 by elution with benzene–ethanol (10:1). The solvent was removed from the eluate in vacuo to give 2 g (81%) of nitrile IV as a slightly yellowish, uncrystallizable, very viscous mass. Nitrile IV was characterized as the picrate with mp 155-156° (orange needles from ethanol–ether). Found: C 58.0; H 3.8; N 14.7%. $C_{17}H_{14}N_2 \cdot C_6H_3N_3O_7$. Calculated: C 58.0; H 3.6; N 14.8%.

α-(3-Indolyl)-β-phenylpropionic Acid (V). Crude nitrile IV from the decarboxylation of 2.9 g (0.01 mole) of acid IIIb was dissolved in 5 ml of ethylene glycol, and the solution was transferred to a 50-ml flask; the test tube was rinsed out with another 5 ml of ethylene glycol, and the rinse was added to the flask. A 1.5-g (0.027 mole) sample of KOH was added, and the mixture was refluxed on a metal bath at a bath temperature of 180-185° for 3-4 h until ammonia evolution ceased. The mixture was then cooled, 80 ml of water was added, and the mixture was washed with two 30-ml portions of ether. The aqueous layer was acidified with concentrated HCLand extracted with two 100-ml portions of ether. The ether extracts were washed with two 100-ml portions of water and dried with anhydrous $MgSO_4$. The ether was removed by distillation to give 1.6 g (60%) of acid V with mp 157-159° (from aqueous methanol). Found: C 77.1; H 5.8; N 5.1%. $C_{17}H_{15}NO_2$. Calculated: C 77.0; H 5.7; N 5.3%. IR spectrum: 1710 (C=O), 2500-2800 (COOH), 3400 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 223 (4.59); 283 (3.90); 290 nm (3.65). PMR spectrum (in $CDCl_3$): q 3.25, q 3.58 ($CH_2C_6H_5$) t 4.30 (CHCOOH), and s 8.25 (NH).

LITERATURE CITED

1. O. D. Shalygina, L. Kh. Vinograd, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 795 (1975).
2. R. Barlow, Introduction to Chemical Pharmacology [Russian translation], Moscow (1959), p. 231.
3. J. Dockx, Syntheses, (1973), p. 441.
4. V. S. Rozhkov, Yu. I. Smushkevich, T. A. Kozik, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 1502 (1974).